Lectin Binding to Human Gastric Adenocarcinomas and Adjacent Tissues

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The binding of lectins to paraffin sections of nine gastric carcinomas and adjacent mucosa was examined by fluorescence microscopy. A battery of nine lectins was employed, and both intestinal and diffusely infiltrating tumors were tested. Wheat germ agglutinin and *Ricinus communis* agglutinin I appeared to bind to both mucus and nonmucus glycoproteins; these lectins labeled tumor cells, benign epithelial cells, and nonepithelial tissues strongly and consistently. Peanut agglutin, soybean agglutinin, *Dolichos biflorus* agglutinin, *Bandeiraea simpifolica* agglutinin, and *Ulex europaeus* agglutinin I bound extensively to mucosubstances in vacuoles and apices of benign epithelial cells but often bound to tumor cells focally and in some cases not at all. Neuraminidase digestion enhanced lectin staining in some tumors; but in others, especially those of the diffusely infiltrating type, neuraminidase digestion did not enhance the staining of tumor cells. The results suggest that the decrease in the proportion of tumor cells labeling with lectin relative to superficial epithelial cells can be due either to the oversialylation of mucoproteins or to the loss of glycosylating enzyme activity. Concanavalin A did not bind to mucosubstances in the vacuoles or apices of benign epithelium, but bound to mucus vacuoles of metaplastic epithelium and to coarse cytoplasmic granules in two of the tumors examined. This suggests either the abnormal addition of mannose to mucus glycoprotein or the production of a distinct glycoprotein by some gastric tumors. (Am J Pathol 1985, 119:279–287)

THE PRODUCTION of abnormal glycoproteins by gastric adenocarcinomas has been the subject of continuing investigation for many years. The secretions of gastric carcinomas consist in large part of mucus glycoprotein[1] and differ from the secretions of normal gastric mucosa in the proportions of the major monosaccharides they contain.[2,3] In addition, there are differences between carbohydrate blood group antigens present in tumor and those present on red blood cells.[4–7] These differences most often consist of deletions of ABH antigens from tumor or the inappropriate expression of the ABH precursor antigen, I (Ma) in tumors from patients who are secretors of ABH antigens[4–6] and who would not be expected to express I (Ma) in gastric tissue. Although less common, expression of A antigen in tumors from blood group B and O patients has also been reported.[5–7]

The carbohydrates in gastric carcinoma may be analyzed by cytochemical methods with the use of lectins,[8] glycoproteins which bind to specific carbohydrate residues.[9,10] While relatively uniform binding of lectin to normal gastric surface epithelium has been observed, gastric carcinomas have been found have heterogeneous lectin binding patterns.[11–13] The molecular mechanisms responsible for this heterogeneity and the relationships between lectin binding patterns and tumor cell morphology and function are not established. The purpose of the present study was to correlate the distribution of lectin-binding carbohydrates with the gross and microscopic anatomy of gastric carcinoma, to determine what differences may occur between carcinoma and adjacent mucosa, and to investigate mechanisms by which abnormal glycosylation might occur in carcinoma of the stomach.

Materials and Methods

Gastric carcinomas from 9 patients with tumors of the cardia, or antrum were studied. The gross and light-microscopic features of these tumors are summarized in Table 1. Four diffuse and five intestinal types were present among the tumors examined. Well, moderately,

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Table 1—Gastric Carcinoma: Anatomic Features and Patient Blood Groups

Case	Site of origin of main tumor	Histologic type	Blood group
1	Antrum	Diffuse, signet ring type	B+
2	Cardia	Diffuse, signet ring type	A+
3	Body	Diffuse, signet ring type	A+
4	Cardia	Diffuse, mucinous	O+
5	Cardia	Intestinal, well differentiated	B+
6	Cardia	Intestinal, well differentiated	A+
7	Cardia	Intestinal, well differentiated	AB+
8	Body	Intestinal, poorly differentiated	O+
9	Antrum	Intestinal, poorly differentiated	AB+

and poorly differentiated tumors were among the intestinal types. Tissue from the tumors was fixed in phosphate-buffered formalin (3.7%), embedded in paraffin, and sectioned at 6 μ. Sections of tumor stained with hematoxylin and eosin (H&E) were examined and classified according to the scheme of Lauren.[14]

A battery of lectins listed in Table 2 was used to stain paraffin sections of tumor and adjacent nonneoplastic mucosa, which in some cases contained areas of intestinal metaplasia. The sugar specificities and inhibitory carbohydrates of lectins used in this study are also listed in Table 2.

The staining procedure consisted of deparaffinizing sections which had been attached to glass slides with a resin glue and rehydrating them through graded alcohols. Sections were stained with biotin-conjugated lectin (Vector Laboratories, Burlingame, Calif) in 10 mM HEPES, 0.15 M NaCl, 0.1 mM $CaCl_2$, 0.04% NaN_3, and, in the case of Con A, 1 mM $MnCl_2$ for 30 minutes. The sections were then washed three times in phosphate-buffered saline (PBS), incubated for 30 minutes at room temperature with fluorescein-conjugated avidin and washed again with PBS. Nuclei were counterstained with ethidium bromide[15] at a concentration of 1–3 μg/ml in PBS for 15–20 seconds. This polycyclic dye intercalates into double-stranded nucleic acids with the bound dye emitting an orange fluorescence when examined with appropriate filters, which contrasts well with the green fluorescence of fluorescein isothiocyanate (FITC). The stained tissue was examined with an Olympus BHA fluorescence miscroscope equipped with a 100-watt mercury bulb for epifluorescence illumination with an FITC interference excitation filter, a DM 500 dichroic mirror, and a 0-515 barrier filter. In the counterstained sections the relationship of lectin-binding carbohydrate to tumor was well visualized. The percentage of tumor cells appearing to contain or to be juxtaposed to labeled carbohydrate was estimated in increments of 10%. Control sections were stained with lectin in the presence of an excess of the appropriate inhibitory carbohydrate (see Table 2) or with fluorescein-conjugated avidin only. Results were considered positive only in the absence of staining of control sections.

Neuraminidase digestions were performed on sections prior to staining with selected lectins to expose cryptic sugar residues hidden by sialic acid. Enhancement of staining by neuraminidase digestion was tested on sections stained with BSA I, SBA, DBA, PNA, and UEA I. The digestion procedure was performed on deparaffinized sections which had been washed with 0.1 M sodium acetate, pH 5.0. Sections were incubated at 37 C for 90 minutes with neuraminidase from Cl. perfringens (Type V, Sigma Chemical Co., St. Louis, Mo) at a concentration of 2 mg/ml (0.86 U/mg versus NAN-lactose) in 0.1 M sodium acetate, pH 5.0, and 0.04 M $CaCl_2$. The enzymatic reaction was terminated by washing the sections thoroughly in water and in PBS, and the sections were then stained with lectin and ethidium bromide as described above.

Table 2—Sugar Specificities and Inhibitory Carbohydrates of Lectins

Lectin	Carbohydrate specificity[10]	Inhibitory sugar
Arachis hypogaea (peanut agglutinin, PNA)	β-D-Gal-(1→3)-D-GalNAc-	D-Gal
Bandieraea simplicifolia I (BSA I)	α-D-Gal-	Methyl-α-D-Gal
Conavalia ensiformis (concanavalin A, Con A)	α-D-Man-	Methyl-α-D-Man
Dolichos biflorus (DBA)	α-D-GalNAc-	GalNAc
Glycine max (soybean agglutinin, SBA)	α-D-Gal/NAc-	GalNAc
Ricin communis 120 (RCA I)	β-D-Gal-	Lactose
Triticum vulgaris (wheat germ agglutinin, WGA)	β-D-Glc-(1→4)--D-GlcNAc-NeuNAc-	N, N'-Diacetylchitobiose
Ulex europaeus I (UEA I)	α-L-Fuc-	L-Fuc

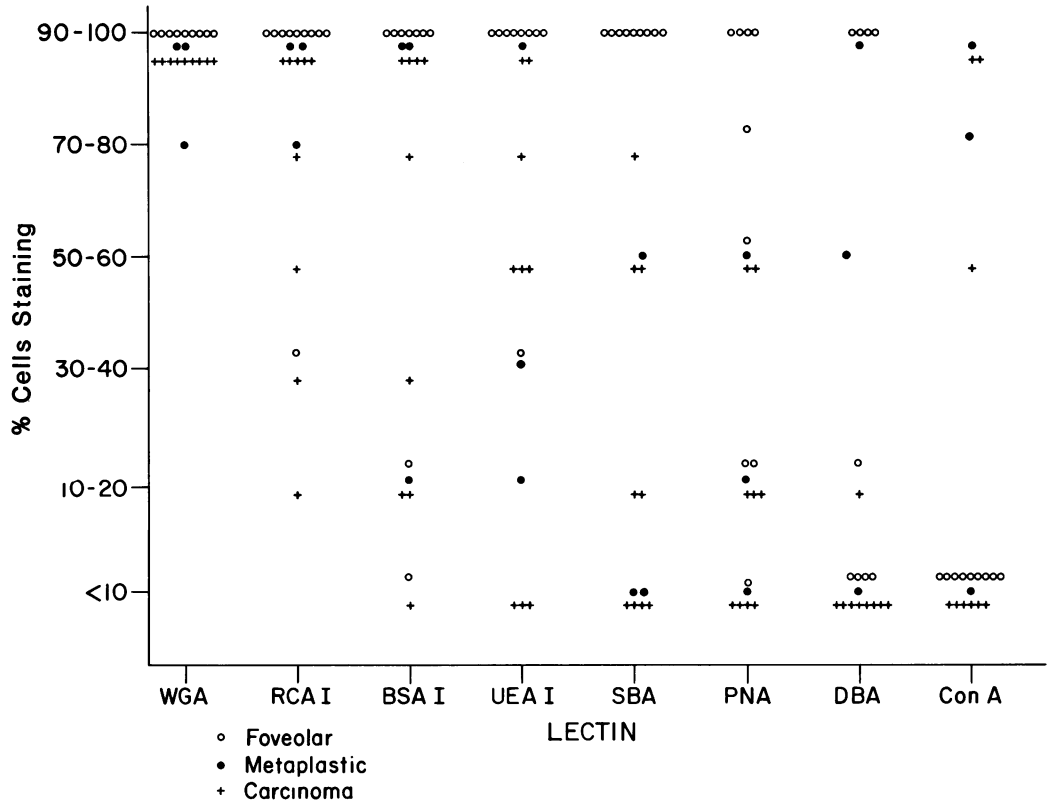

Figure 1—Lectin binding to gastric carcinoma cells and adjacent epithelium. The percentage of cells staining with lectin was estimated by microscopic inspection of paraffin sections (see text). In the case of Con A, weak diffuse staining of epithelial cell cytoplasm was observed, but this level of staining was observed as background throughout the tissue sections and the staining recorded in this diagram refers only to intense labeling of discrete cytoplasmic structures in excess of background levels.

Results

The proportions of neoplastic and nonneoplastic epithelial cells labeled with the various lectins are summarized in Figure 1.

General Observations

Lectin binding to normal mucosa adjacent to tumor was well ordered and consistent. WGA and RCA I appeared to bind extensively both to mucus and to nonmucus glycoproteins (see below). In sections of normal mucosa stained with BSA I, PNA, SBA, DBA, and UEA labeling was more closely, but not exclusively, restricted to mucus vacuoles and apical membranes of mucus epithelium (Figure 2A). Exceptions to the general restriction of labeling to mucus epithelial vacuoles and apical membranes by these lectins included the occasional staining of Golgi apparatus of epithelial cells by SBA (Figure 2B), the staining of parietal cell cytoplasm by DBA, and weak and inconsistent staining of endothelium by UEA I. In sections stained without neuraminidase digestion, there was no staining of endothelium with PNA or SBA; but following neuraminidase digestion, bright, diffuse linear staining along endothelial surfaces was observed with these lectins. Neuraminidase digestion did not appear to enhance UEA I staining of endothelium. Finally, Con A stained stromal tissues and cytoplasm of many cell types, especially plasma cells, but did not stain mucus vacuoles of superficial epithelial cells.

Lectin binding in metaplastic epithelium differed from normal in that mucus vacuoles and apical membranes of intestinal type epithelial cells (Figure 2C) stained less consistently than superficial gastric epithelium (Figure 1). There was a diminution of staining with most of the lectins tested, but in sections stained with Con A there was an increase in the proportions of intestinal epithelial cells labeled in comparison with normal superficial gastric epithelial cells.

Lectin binding to tumor cells appeared disorderly and inconsistent and varied with the lectin applied and with the differentiation of the tumor. Intestinal type tumors showed binding along the apical surfaces (Figure 3A) and sometimes along the basilar or lateral margins of tumor cells. Also in intestinal type tumor, cytoplasmic

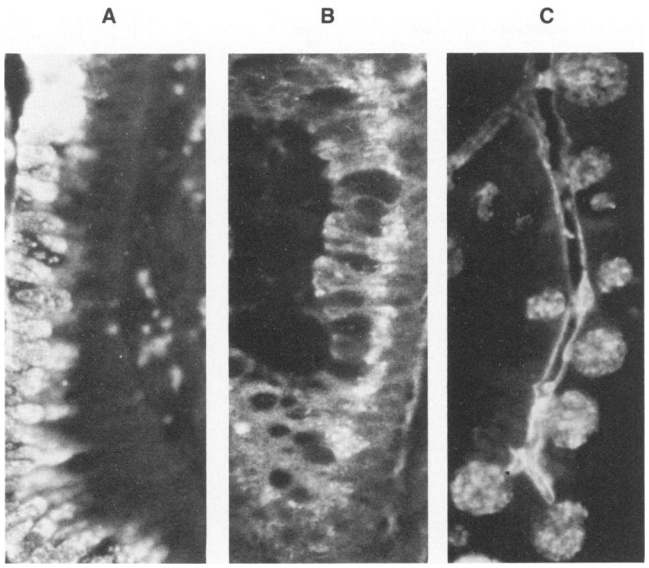

Figure 2—Staining patterns of nonneoplastic epithelia. **A**—Normal foveolar epithelium stained with WGA. There is strong staining of supranuclear vacuoles and along apices of cells. (×730) **B**—Metaplastic epithelial cells stained with SBA. The Golgi apparatus is strongly labeled. (×730) **C**—Metaplastic epithelial cells stained with DBA. There is strong labeling of mucus vacuoles and apices of absorptive cells. (×730)

vacuoles and granules (Figure 3B) were sometimes found in the tumor cells, and some of these tumors contained focal areas with large amounts of extracellular staining (Figure 3C). In diffusely infiltrating tumors lectin-binding carbohydrate could be found in cytoplasmic vacuoles (Figure 3D), along the plasma membranes, and in the extracellular space of the tumor, but there was less distinct polarity of staining than was observed in intestinal tumors.

The most intense labeling and greatest frequency of positive cells was observed with WGA, followed in order by RCA I, BSA I, UEA I, SPA, PNA, Con A, and DBA (Figure 1). In many cases, there was a diminution in the proportion of lectin-positive neoplastic cells, compared with adjacent mucus epithelium. While mucus vacuoles and apices of normal foveolar epithelial cells usually reacted strongly with UEA I, SBA, DBA, PNA, and BSA I, all or large proportions of tumor cells were negative when tested with these lectins (Figure 1). Often tumor cells which were labeled with these lectins occurred in small clusters, while broad areas in the same tumor failed to stain. This reduction in staining relative to normal foveolar epithelium was particularly marked in diffusely infiltrating tumors, and among these were tumors in which only a small proportion of or no tumor cells were labeled with any of these lectins (Figure 4).

The frequent absence or diminution of staining with the mucus-specific lectins in tumor as compared to nonneoplastic mucus epithelium suggested that either the lectin-reactive carbohydrate is deleted from the complex carbohydrate chains of the neoplastic cells or that the lectin-reactive group of the carbohydrate is covered with other moieties, perhaps sialic acid. To test which of these alternatives might be correct, sections were predigested with neuraminidase and stained with lectin as described above. This procedure considerably enhanced staining of many of the tumors (Figure 5A and B) but failed to enhance staining in others. Staining of tumors which were of the diffusely infiltrating type was less frequently enhanced by neuraminidase digestion than was that of those of the intestinal type (Figure 6).

Reactions of Specific Lectins

Labeling reactions of specific lectins are described below.

WGA

All neoplastic and nonneoplastic mucus epithelium, including that of cardial and pyloric glands, stained brightly with this lectin. There was also considerable membrane staining of nonepithelial cells as well. The pattern of staining of tumors varied with the histologic appearance of the tumor, as described above.

RCA

RCA also bound to most neoplastic and nonneoplastic epithelium but, in contrast to WGA, did not bind cardial or pyloric glands. Membrane staining of nonepithelial cells was again noted with this lectin, and there was rather intense staining of extracellular matrix as well.

BSA I

Little staining of tissue other than epithelial cells was observed in sections stained with BSA I. Neuraminidase pretreatment enhanced BSA I binding to well-

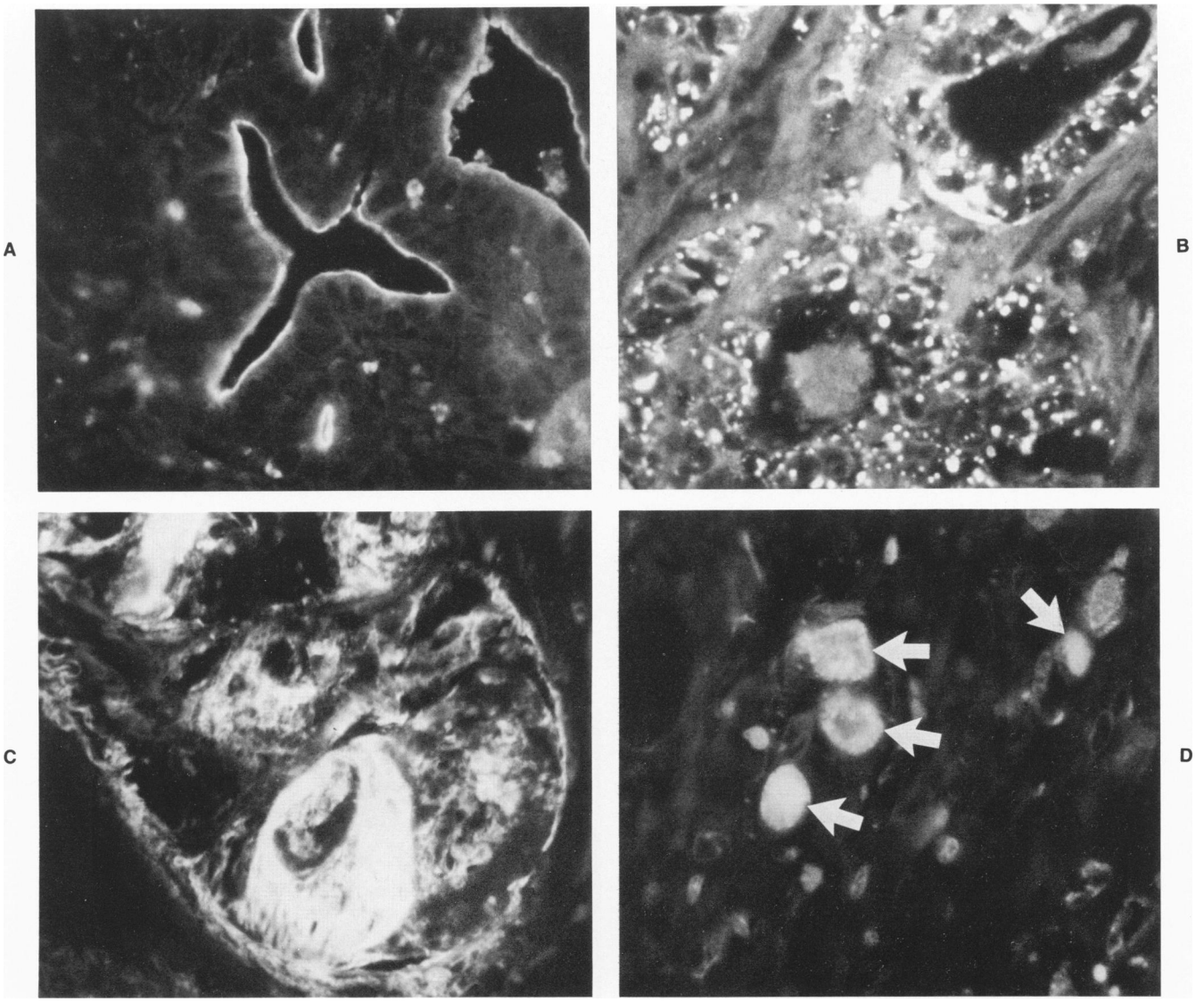

Figure 3—Staining patterns of gastric carcinomas. **A**—Apical labeling of well-differentiated adenocarcinoma with DBA. (×370) **B**—Coarse granular cytoplasmic labeling with Con A of an intestinal adenocarcinoma of the cardia. (×730) **C**—Extensive extracellular staining of mucinous material juxtaposed to carcinoma cells. (×180) **D**—Vacuoles (*arrows*) of a signet ring carcinoma labeling strongly with SBA after neuraminidase digestion. Ovoid nuclei stained weakly with ethidium bromide are present in the background. (×730)

differentiated cancers in most cases. However, a distinct decrease of staining was observed with neuraminidase digestion in three tumors, two of which were of the poorly differentiated, diffuse type.

SBA and DBA

Although these two lectins are reported to have similar binding specificities, their tissue staining patterns differed somewhat. Staining of foveolar cell vacuoles was always pronounced in sections stained with SBA but was often focal or absent in sections stained with DBA. Similarly, there was diffuse or extensive focal staining of metaplastic epithelium stained with SBA, but in 2 of 3 cases, metaplastic epithelium was negative or sparsely and focally positive with DBA. As noted above, SBA frequently stained the focal Golgi apparatus of metaplastic goblet cells. Parietel cell cytoplasm stained with DBA, but no other tissue stained with either of these lectins. Staining of tumor was less extensive with these lectins than was staining of adjacent nonneoplastic epithelium, and in some tumors the sharp contrast between neoplastic and nonneoplastic epithelium was striking. Staining of tumor with SBA was usually augmented by prior digestion of the tissue section with neuraminidase (Figure 5), which suggested that increased sialylation of tumor mucus was responsible

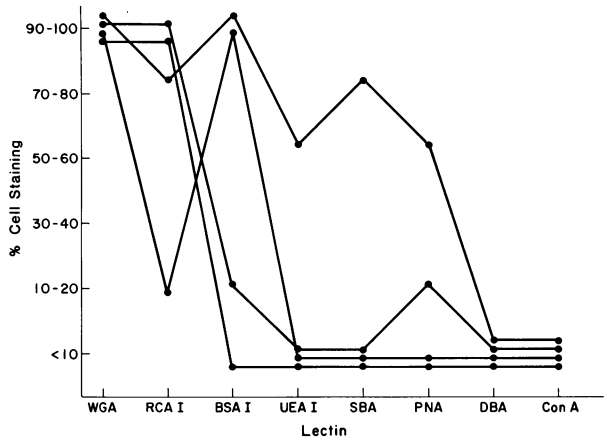

Figure 4—Lectin binding of diffusely infiltrating adenocarcinomas. In this chart each line represents a single tumor. Three of the four tumors tested were negative or weakly positive with most of the lectins tested, including those with preferential specificity for Gal, GalNAc, Fuc, and Man.

for the loss of SBA-binding activity in most tumors. Augmentation of staining was less frequent with DBA.

Although SBA[16,17] and DBA[18] have blood group A specificity, no correlation between patient blood group and staining of either normal or neoplastic tissue was observed. All patients, regardless of blood type, showed strong staining of normal mucus-secreting epithelium, and three of the four tumors which did not bind SBA in tissue sections were from type A patients. Tumors of both type O patients in the study expressed considerable SBA-binding in tissue sections.

PNA

Staining was inconsistent and often focal in both neoplastic and nonneoplastic epithelium stained with PNA. No binding was noted in nonepithelial tissues.

Neuraminidase digestion enhanced tissue binding of PNA in metaplastic epithelium and in well-differentiated intestinal carcinomas but, with the exception of one case, did not enhance staining of diffuse carcinomas, which remained weakly positive (Figure 5).

UEA I

Staining of tumor with UEA I was often absent or diminished in comparison with staining of normal foveolar epithelium. Labeling was not enhanced by neuraminidase digestion, suggesting that the loss of lectin binding reactivity was not due to sialylation of terminal fucose residues. The staining patterns of positive

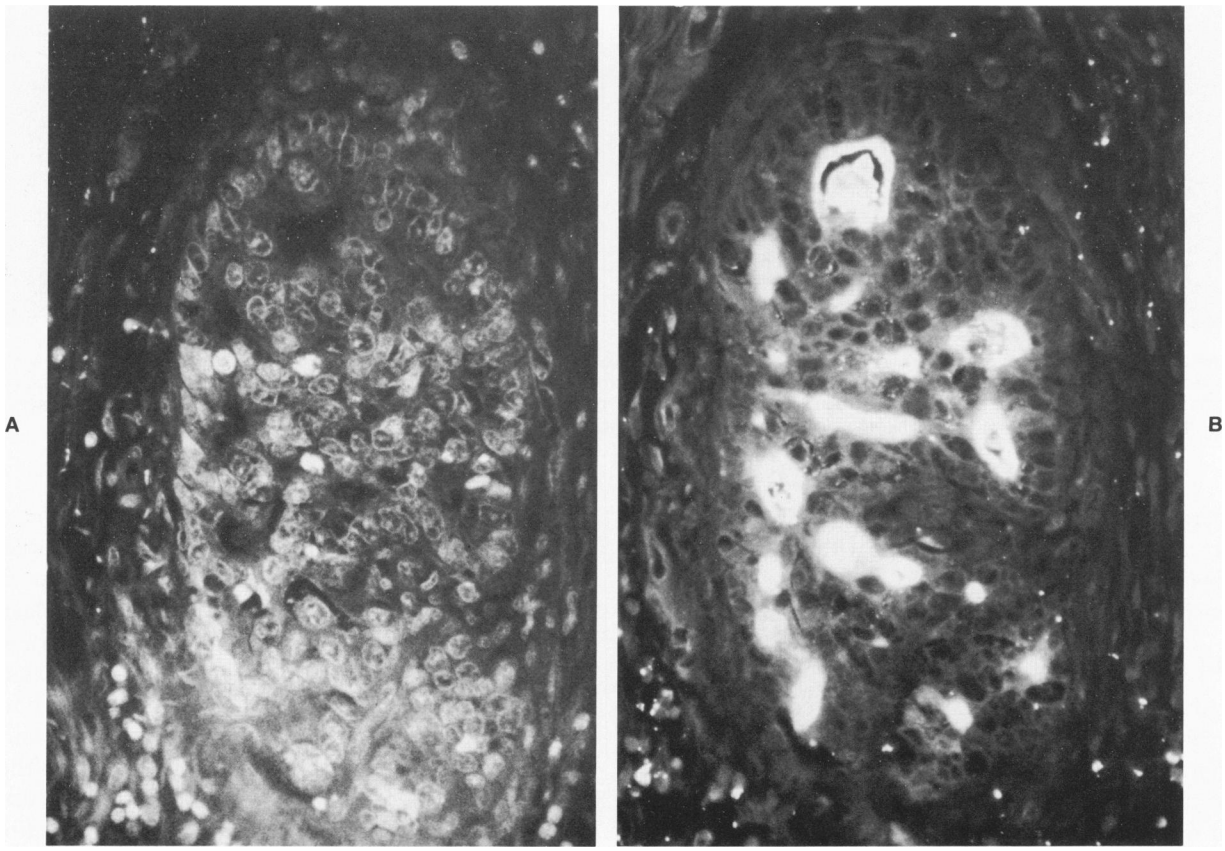

Figure 5—Enhancement of lectin binding after neuraminidase digestion. **A**—Section of tumor stained with SBA without prior enzymatic digestion. **B**—Parallel section stained with SBA after digestion with neuraminidase. Intense staining at apices of tumor cells and in lumens of tumor ducts is present in this section. Weakly staining ovoid nuclei are present in the background in both sections.

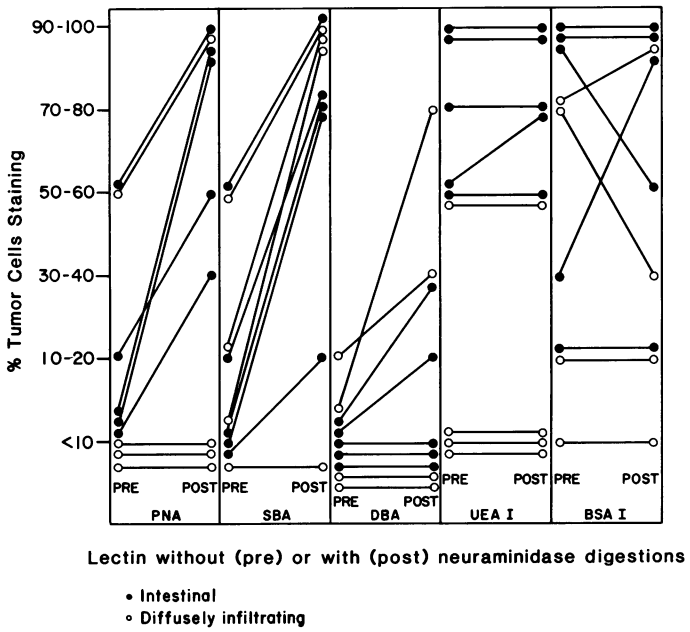

Figure 6—Enhancement of lectin binding to gastric carcinoma cells after digestion of parallel sections with neuraminidase. Enhancement of binding was more frequently observed in intestinal type tumors than in diffusely infiltrating tumors in sections stained with PNA and SBA. Little enhancement of labeling of either type of tumor was observed in sections stained with UEA I.

cells were similar to those seen with other lectins with apical staining of intestinal type tumors and diffuse membrane, granular cytoplasmic, and stromal staining of single-cell infiltrative tumors as noted above. There was weak focal staining of vascular endothelium but no staining of any other nonepithelial tissue.

Although UEA I has O blood group specificity (reviewed by Goldstein and Hayes[10]), no correlation between blood group and lectin localization in tissue could be discerned in this study. In all cases, there was staining of normal-appearing mucus epithelium, and there was considerable staining of tumor from group A, AB, and B patients. Both the two type O patients showed extensive focal staining of tumor.

Con A

A generalized stromal and cellular background staining was usually present in sections stained with Con A, and the cytoplasm of plasma cells was particularly bright. Among the epithelial cells there was moderately intense granular cytoplasmic staining of specialized fundic epithelial cells, but foveolar vacuoles were negative, and cell cytoplasm stained weakly, that is, with the level of fluorescence in these cells indistinguishable from the stromal background. Staining of the vacuoles of metaplastic goblet cells and tumor cells with this lectin was variable. In most tumors there was no staining of mucus glycoprotein, but weak diffuse labeling of cellular nonmucus glycoprotein was usually observed. Two tumors (one cardial and one pyloric) were noteworthy, in that they showed strong and distinct staining of cytoplasmic granules (Figure 2B).

Discussion

In normal mucosa, lectin binding was constant and well ordered, with heavy staining of mucus vacuoles and apices of epithelial cells. In sections stained with BSA I, SBA I, DBA, PNA, and UEA I, labeling was largely restricted to mucus-secreting epithelial cells. The heavy binding of these lectins to epithelium is consistent with the biochemical finding of large amounts of Gal, GalNAc, and Fuc in mucus glycoproteins.[2,19] In contrast, WGA and RCA I labeled both epithelial and nonepithelial tissues strongly. These lectins thus appear to have specificities for determinants that are more broadly distributed in the tissues than the previously mentioned lectins. In biochemical studies, WGA has been found to bind both β-D-GlcNAc-(1→4) and β-D-GlcNAc and sialic acid as well.[20] Sialic acid is a terminal sugar commonly found in glycoproteins of cells and tissues of many types.[2] Finally, Con A failed to stain mucus vacuoles and apices of epithelial cells but stained cytoplasm of epithelial cells as well as many nonepithelial cells and extracellular stroma. This finding also is consistent biochemical results, because mannose is found to be present only in trace quantities in mucus glycoproteins.[19]

Lectin binding to metaplastic mucus epithelium was somewhat less consistent than lectin binding to normal foveolar epithelium. A proportion of metaplastic epithelial cells failed to stain with Gal-, GalNAc-, and Fuc-binding lectins (see Figure 1), and Con A binding was observed in mucus vacuoles in 2 of the 3 cases studied.

In contrast to staining patterns in benign mucosa, those in gastric carcinoma were greatly disordered, and lectin-binding carbohydrate was found not only in well-

formed mucus vacuoles but also in small granules, along cell membranes, and within the stromal tissues as well. Many tumor cells appeared to be encased in a thick coating of lectin-binding material.

Staining of carcinoma cells with SBA, DBA, PNA, and UEA I was less frequent than staining of non-neoplastic epithelium, and in some sections the reduction of lectin binding in the tumor was quite striking. This reduction of staining may have been due either to absence of glycosylating enzyme in tumor cells or to covering of certain residues with other sugars such as sialic acid. That both mechanisms are involved is suggested by the marked enhancement of staining induced by neuraminidase digestion that was observed in sections of some gastric tumors and the failure of neuraminidase digestion to enhance lectin staining of other tumors, primarily of the diffusely infiltrating type (Figure 5). Presumably those tumors in which staining was enhanced by neuraminidase digestion contained residues that were covered by sialic acid and therefore unavailable for lectin binding. The excess sialylation and impaired expression of carbohydrate antigen has been previously described in human breast tumors.[22] On the other hand, those tumors in which lectin staining was not enhanced by neuraminidase digestion may have lacked the glycosylating enzymes necessary for the normal sequential addition of carbohydrate chains to mucus, perhaps as a result of genetic disarrangement. That this disarrangement may involve the coding loci for several enzymes is suggested by the tendency for deletion of several lectin-binding carbohydrates to occur simultaneously in a single tumor (Figure 3).

Two tumors, one from the cardia and one from the pylorus, showed strong and distinct Con A staining of cytoplasmic granules, whereas this pattern was not observed in normal epithelium. Con A binds principally to mannose, which is virtually absent from mucus glycoprotein. Whether the binding of Con A to a subset of gastric carcinomas reflects simply the abnormal glycosylation of mucus glycoproteins or the production of a glycoprotein distinct from mucus glycoprotein remains to be determined. It is of interest that in some cases of intestinal metaplasia Con A-positive mucus vacuoles were observed, which suggests that progression from normal to mucosa metaplasia to anaplasia may be accompanied by the abnormal glycosylation of mucus glycoproteins. The presence of Con A-positive material in cancer from pyloric and cardial areas of the stomach also suggests that these tumors may have differentiated into cell types more analogous to the cells of the pyloric or cardial glands, which were strongly Con A-positive, than to the superficial mucus epithelial cells, which were Con A-negative.

The present results are generally in agreement with previously reported studies of lectin binding in gastric carcinoma.[11-13] However, in the current study, neuraminidase digestion was found to enhance lectin binding, particularly PNA binding, in several intestinal tumors; whereas in a previous study,[12] neuraminidase failed to enhance PNA binding in intestinal type tumors, which were already strongly PNA positive, but did enhance PNA binding to signet ring tumor. The source of this discrepancy is not obvious, and study of additional cases may help to resolve the issue.

Three of the lectins (SBA I, DBA, and UEA I) used in this study have specificity for blood group substances. The localization of these lectins in apparently normal mucosa, in metaplastic epithelium, and in tumor bore no detectable relationship to the blood group and type of the patient. It thus appears that the lectins used in this study react with a range of determinants broader than blood group antigens and that antisera are more appropriate reagents than lectins for studying the expression of blood group antigens in gastric mucosa.

The variation in expression of carbohydrate residues in gastric adenocarcinoma demonstrated in this study presumably reflects abnormal expression of glycosyl transferase expression. Changes in lectin-binding carbohydrate expression should suggest which transferase enzymes are abnormally expressed, and it should be possible to directly measure the enzyme activities in tissue homogenates.

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